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Allylcyanation of Alkynes: Regio- and Stereoselective Access to Functionalized Di- or Trisubstituted Acrylonitriles

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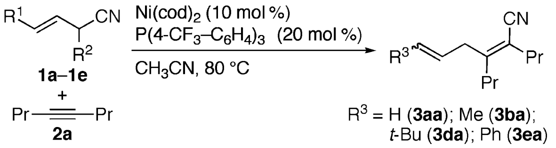
Direct cleavage of a R−CN bond followed by reconnection of both R and CN with two carbons in unsaturated carbon−carbon bonds, namely the carbocyanation reaction,[1] provides ready access to highly functionalized nitriles from simple ones with perfect atom economy and, thus, should be of great synthetic value. We report herein a new carbocyanation of alkynes using allyl cyanides. The present allylcyanation reaction allows simultaneous installation of a linear C_3 having a terminal double bond or carbonyl group and CN to alkynes having various functional groups in highly regio- and stereoselective manners.

To probe the viability of the allylcyanation reaction, we initially surveyed a set of nickel catalysts for the reaction of allyl cyanide (**1a**: 4.0 mmol)[2] and 4-octyne (**2a**: 1.0 mmol) in CH_3CN at 80 °C. Of the ligands we examined with $Ni(cod)_2$ (10 mol %), $P(4-CF_3-C_6H_4)_3$ was found to be optimal to give the expected *cis*-adduct, (*Z*)-2,3-dipropyl-2,5-hexadienenitrile (**3aa**), exclusively in 78% yield (entry 1 of Table 1).[3] Under these conditions, both 3-pentenenitrile (**1b**) and 2-methyl-3-butenenitrile (**1c**) also reacted with **2a** to give the same crotylcyanation product **3ba** as a mixture of stereoisomers (entries 2 and 3), suggesting a π-allylnickel intermediate (vide infra). No detectable amount of the adduct derived from the addition at the congested carbon was observed. The reactions of (*E*)-5,5-dimethyl-3-hexenenitrile (**1d**) and (*E*)-4-phenyl-3-butenenitirile (**1e**) gave the corresponding linear adducts **3da** and **3ea** as stereochemically pure forms (entries 4 and 5).

The addition of α-siloxyallyl cyanide **1f** (1.5 mmol), which is readily available from acrolein and Me_3SiCN, across **2a** (1.0 mmol) also proceeded at the γ-carbon exclusively to give aldehyde **3fa** after acidic hydrolysis (Scheme 1).[4] Formation of a silyl enol ether as an initial product of the present catalytic reaction was proved by using α-*tert*-butyldimethylsilyloxyallyl cyanide (**1g**), affording the corresponding silyl enol ether **3ga** in 87% yield as a mixture of stereoisomers.

Other α-siloxyallyl cyanides having a substituent at the α- or β-position underwent the addition reaction across **2a**, giving the corresponding aldehydes or ketones in good yields (entries 1−4 of Table 2), whereas the reactions of γ-substituted ones such as (*E*)-4-phenyl-2-(trimethylsilyloxy)-3-butenenitrile turned out to be sluggish. Alkynes other than **2a** were also examined using **1f**. 2-Butyne (**2b**) reacted similarly albeit in a lower yield (entry 5); whereas the reaction of 2-pentyne (**2c**) showed poor regioselectivity (entry 6), 1-phenylpropyne (**2d**) gave an isomer having a larger phenyl group at a cyanosubstituted carbon preferentially (entry 7). Terminal alkynes also underwent the carbocyanation reaction in highly regioselective manners (entries 8−13) even on a gram-scale (entry 8).[5] Functional groups such as chloro, ester, and phthalimide were tolerated (entries 10−12).

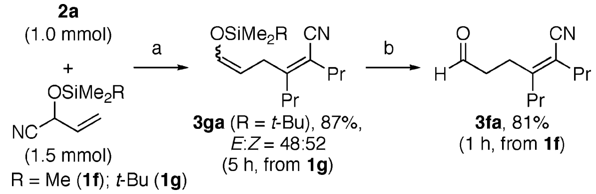
Table 1. Nickel-Catalyzed Carbocyanation of 4-Octyne (**2a**) Using Allyl Cyanides[a]



entry	R^1	R^2	time (h)	**3** (5*E*:5*Z*)[b]	yield (%)[c]
1	H	H (**1a**)	8	**3aa** (−)	78
2	Me	H (**1b**)	17	**3ba** (83:17)	55
3	H	Me (**1c**)	17	**3ba** (85:15)	69
4[d]	*t*-Bu	H (**1d**)	18	**3da** (>99:1)	49
5[d]	Ph	H (**1e**)	18	**3ea** (>99:1)	86

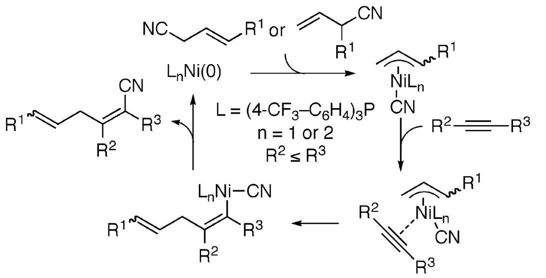
[a] All reactions were carried out using an allyl cyanide (4.0 mmol), **2a** (1.0 mmol), $Ni(cod)_2$ (0.10 mmol), $P(4-CF_3-C_6H_4)_3$ (0.20 mmol) in CH_3CN (2.0 mL) at 80 °C. [b] Determined by ^1H NMR and/or GC analysis of a crude and/or purified product. [c] Isolated yields based on **2a**. [d] The reaction was carried out in CH_3CN (1.0 mL).

Scheme 1. Carbocyanation of **2a** Using α-Siloxylallyl Cyanides[a]



[a] Reagents and Conditions: (a) $Ni(cod)_2$ (10 mol %), $P(4-CF_3-C_6H_4)_3$ (20 mol %), CH_3CN, 80 °C; (b) 1 M HCl aq, THF, 0 °C to rt overnight.

Scheme 2. Plausible Mechanism of Allylcyanation of Alkynes



On the basis of the observed experimental results, we consider that the catalysis would be initiated by oxidative addition of a C−CN bond to Ni(0)[6−9] to give at first a π-allylnickel intermediate. The primary carbon of the allyl group would migrate to the less hindered *sp*-carbon of an alkyne[10] to give an alkenyl-Ni(II)-CN intermediate, which would afford a *cis*-allylcyanation product and regenerate Ni(0) upon reductive elimination (Scheme 2).

Synthetic versatility of the carbocyanation products is demonstrated briefly in Scheme 3. The cyano group of **3aa** was reduced to give the corresponding substituted acrolein **5** or allyl alcohol **6**, whereas the formyl group of **3fa** was transformed to afford alcohol **7** or 2,6-heptadienenitrile **8**, a formal homoallylcyanation product.[11] Aldol-type condensation of **3fa** with formaldehyde gave α-functionalized acrolein **9** in 83% yield.[12]

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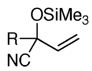
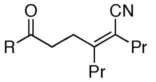
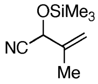
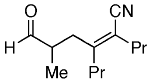
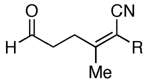
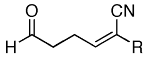
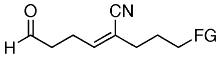
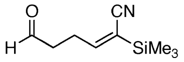
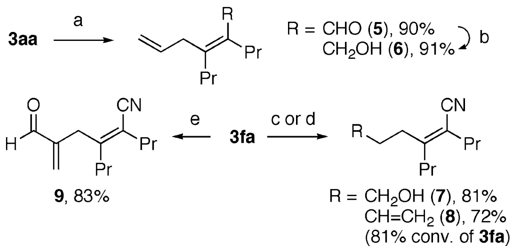
Table 2. Nickel-Catalyzed Carbocyanation of Alkynes Using α-Siloxyallyl Cyanides[a]

entry	allyl cyanide	alkyne	time (h)	major product, yield (%)[b]
				
1[c]	R = Me (**1h**)	**2a**	2	R = Me (**3ha**), 71%
2[c]	Et (**1i**)	**2a**	3	Et (**3ia**), 81%
3[c]	Ph (**1j**)	**2a**	2	Ph (**3ja**), 54%
4	 **1k**	**2a**	12	 **3ka**, 69%
		$\mathrm{Me}{-}{\equiv}{-}\mathrm{R}$		
5	**1f**	R = Me (**2b**)	1	R = Me (**3fb**), 58%
6	**1f**	Et (**2c**)	1	Et (**3fc**), 58% (61:39)[d]
7	**1f**	Ph (**2d**)	1	Ph (**3fd**), 70% (93:7)[d]
		${\equiv}{-}\mathrm{R}$		
8[e]	**1f**	R = Hex (**2e**)	1	R = Hex (**3fe**), 74%[f] (92:8)[d]
9[g]	**1f**	*t*-Bu (**2f**)	1	*t*-Bu (**3ff**), 61%[h] (>99:1)[d]
		${\equiv}{-}(\mathrm{CH_2})_3\mathrm{FG}$		
10[g]	**1f**	FG = Cl (**2g**)	1	FG = Cl (**3fg**), 78%[h] (95:5)[d]
11[g]	**1f**	CO_2Me (**2h**)	1	CO_2Me (**3fh**), 62%[h] (95:5)[d]
12[g]	**1f**	CH_2NPhth (**2i**)	1	CH_2NPhth (**3fi**), 60%[f] (90:10)[d]
13[g]	**1f**	${\equiv}{-}\mathrm{SiMe_3}$ **2j**	1	 **3fj**, 36%[h] (>99:1)[d]

[a] Unless otherwise noted, all reactions were carried out using an allyl cyanide (1.5 mmol), an alkyne (1.0 mmol), Ni(cod)$_2$ (0.10 mmol), and P(4-CF$_3$−C$_6$H$_4$)$_3$ (0.20 mmol) in CH$_3$CN (1.0 mL) at 80 °C, and crude products were treated with 1 M HCl aq in THF at 0 °C to rt. [b] Isolated yields of an isomerically pure product based on an alkyne. [c] The reaction was carried out in toluene at 120 °C. [d] Ratios to a regioisomer (**4**, structure is shown in Supporting Information) determined by ^{1}H NMR and/or GC analysis of a crude and/or purified product. [e] The reaction was carried out using **1f** (15 mmol) and **2e** (30 mmol). [f] Isolated yields of an inseparable mixture of two regioisomers based on **1f**. [g] **1f** (1.0 mmol) and an alkyne (2.0 mmol) were used. [h] Isolated yields of an isomerically pure product based on **1f**.

Scheme 3. Transformations of Allylcyanation Products[a]



[a] Reagents and Conditions: (a) DIBAL-H, toluene, −78 °C, 1.5 h, then SiO$_2$; (b) LiAlH$_4$, THF, rt, 10 min; (c) NaBH$_4$, MeOH, 0 °C, 1 h; (d) CH$_2$(ZnI)$_2$, THF, rt, 0.5 h; (e) HCHO aq, (CH$_2$)$_5$NH, EtCO$_2$H, *i*-PrOH, 45 °C, 24 h.

In conclusion, we have demonstrated for the first time that allylcyanation of alkynes proceeds successfully under nickel catalysis. The reaction allows one-step synthesis of a diverse range of alkenenitriles having functional groups regio- and stereoselectively. Further efforts to expand the scope of the chemistry to other nitriles and unsaturated compounds are ongoing subjects in our laboratories.

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Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http:/pubs.acs.org.

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(2) Use of a smaller amount of allyl cyanide retarded the reaction presumably due to unidentified side reactions of allyl cyanide during the reaction.

(3) Although detailed mechanistic studies would be necessary to explain electronic effects of a ligand on the present catalysis, oxidative addition of allyl cyanides might not be rate-determining as the step generally requires electron-rich nickel complexes. See also refs 6 and 8. The following results were obtained with other ligands (GC yield): PPh$_3$, 61%; P(4-MeO−C$_6$H$_4$)$_3$, 8%; PMe$_3$, PCy$_3$, and P(*t*-Bu)$_3$, <5%.

(4) The reactions of α-siloxyallyl cyanides are generally cleaner than those of non-oxygenated allyl cyanides **1a**−**1e** presumably due to the improved stability of the corresponding *π*-allylnickel intermediates having a siloxy group.

(5) Use of an excess amount (2.0 equiv to **1f**) of terminal alkynes gave better results as they appeared to undergo competitive trimerization and/or oligomerization in the presence of a nickel catalyst.

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